

EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF 2,4-DP

Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency



2,4-DP

- Chlorophenoxy acid herbicide
 - 2,4 dichlorophenoxy acetic acid (2,4-D)
 - 2,4 dichlorophenoxy butyric acid (2,4-DB)
 - 2,4 dichlorophenoxy propanoic acid (2,4-DP)
 - Structural analogues of the plant hormone auxin
- Uses
 - Broad leaf herbicide: lawns, landscaping, weed control
 - Little agricultural use, home/commercial use not quantified
 - Registered for use in California as salts and esters
- Environmental fate
 - Minimal soil adsorption, breakdown
 - Long (>100 days) half life in ground water



2,4-DP

- Pharmacokinetics
 - High absorption, protein binding, volume of distribution
 - Excreted via kidney largely unchanged
 - Serum half-life 10 hours
- Subchronic, chronic toxicity
 - Hepatotoxicity, kidney toxicity, anemia
 - Induces P450 enzymes, peroxisome proliferator
 - Changes in circulating cholesterol and triglycerides

Animal Developmental Toxicity Studies

Agent	Species	Doses (mg/kg/day)	Reference
2,4-DP	Mouse	0,100,200,300,400,500	Roll & Matthiaschk, 1983
2,4-DP(+)	Mouse	0, 200, 300, 400, 500	Roll & Matthiaschk, 1983
2,4-DP	Rat	0, 10, 30, 100	Litton Bionetics, 1973
2,4-DP	Rat	0, 8, 20, 50, 125	Hazleton, 1980
2,4-DP	Rabbit	0, 12, 30, 75	Hazleton, 1979
2,4-DP(+)	Rat	0, 20, 80, 160	Hellwig, 1993b
2,4-DP(+)	Rabbit	0, 20, 50, 100	Hellwig, 1993a

Animal Developmental Toxicity Studies

Agent	Species	Doses (mg/kg/day)	
2,4-DP	Mouse	0, 100, 200, 300, 400, <u>500</u>	↓ fetal weight ↑ resorptions ↑ postimplant loss ↑ fused ribs ↑ cleft palate ↓ pregnancy weight gain (18%)
2,4-DP(+)	Mouse	0, 200, 300, 400, 500	
2,4-DP	Rat	0, 10, 30, 100	
2,4-DP	Rat	0, 8, 20, 50, 125	
2,4-DP	Rabbit	0, 12, 30, 75	
2,4-DP(+)	Rat	0, 20, 80, 160	
2,4-DP(+)	Rabbit	0, 20, 50, 100	

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2,4-DP	Rat	0, 10, 30, 100	
2,4-DP	Rat	0, 8, 20, 50, 125	
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Animal Developmental Toxicity Studies

Agent	Species	Doses (mg/kg/day)	
2,4-DP	Mouse	0, 100, <u>200</u> , 300, 400, 500	NOAEL, no effects NOAEL
2,4-DP(+)	Mouse	0, <u>200</u> , 300, 400, 500	
2,4-DP	Rat	0, 10, 30, 100	
2,4-DP	Rat	0, 8, 20, 50, 125	
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2,4-DP	Rat	0, 10, 30, <u>100</u>	NOAEL
2,4-DP	Rat	0, 8, 20, 50, <u>125</u>	
2,4-DP	Rabbit	0, 12, 30, 75	
2,4-DP (+)	Rat	0, 20, 80, <u>160</u>	
2,4-DP(+)	Rabbit	0, 20, 50, 100	↓ fetal weight ↓ ossification ↑ extra ribs ↑ hydroureter ↓ pregnancy weight gain (13%)

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2,4-DP	Rat	0, 10, 30, <u>100</u>	NOAEL
2,4-DP	Rat	0, 8, 20, 50, <u>125</u>	NOAEL
2,4-DP	Rabbit	0, 12, 30, 75	
2,4-DP (+)	Rat	0, 20, <u>80</u> , 160	NOAEL
2,4-DP(+)	Rabbit	0, 20, 50, 100	

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			NOAEL
2,4-DP	Rat	0, 10, 30, <u>100</u>	
			NOAEL
2,4-DP	Rat	0, 8, 20, 50, <u>125</u>	
2,4-DP	Rabbit	0, 12, 30, <u>75</u>	(Dutch-belted) ↓ fetal weight 3 fetuses malformed >10% maternal mortality in study
2,4-DP (+)	Rat	0, 20, <u>80</u> , 160	
2,4-DP(+)	Rabbit	0, 20, 50, 100	

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2,4-DP	Rat	0, 10, 30, <u>100</u>	NOAEL
2,4-DP	Rat	0, 8, 20, 50, <u>125</u>	NOAEL
2,4-DP	Rabbit	0, 12, 30, 75	
			NOAEL
2,4-DP (+)	Rat	0, <u>20</u> , 80, 160	(Himalayan) ↑ extra ribs ↓ ossification ↓ decreased maternal weight gain GD 7-9 only
2,4-DP(+)	Rabbit	0, 20, 50, <u>100</u>	

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2,4-DP	Rat	0, 10, 30, <u>100</u>	NOAEL
2,4-DP	Rat	0, 8, 20, 50, <u>125</u>	NOAEL
2,4-DP	Rabbit	0, 12, 30, 75	
2,4-DP (+)	Rat	0, 20, <u>80</u> , 160	NOAEL
2,4-DP(+)	Rabbit	0, 20, <u>50</u> , 100	NOAEL

Female reproductive toxicity

- Two rat multigeneration studies
 - No effects on fertility
 - Perinatal effects at high dose (226 mg/kg/day)
 - Prolonged gestation, dystocia
 - Increased stillbirth , lower litter size at birth, lower birth weight
 - Greater incidence of
 - insufficient maternal care
 - umbilical cord not cut
 - placenta not consumed
 - Parental toxicity
 - Characteristic liver, kidney effects; serum cholesterol changes
 - Lower weight gain (~20% less than controls)
- Chronic and subchronic studies
 - No consistent effects on ovarian weight or pathology

Male reproductive toxicity

- Two rat multigeneration studies
 - No effects on fertility
 - ↓ absolute testes weights F0 and F1 males
- Dominant lethal
 - No effects
- Chronic and subchronic studies
 - 13 week rat study; ↓ absolute and relative testes weights
 - 24 month study; ↑ incidence prostatitis

Summary

- Developmental toxicity;
effects in mice, rabbits, rats.
- Female reproductive toxicity;
peripartum effects in rats.
- Male reproductive toxicity;
effects on testicular weight in rats.

